REMARKS

Upon entry of the forgoing amendment claims 1, 2, 5-7, 10, 17, 18, 20-24, 26-27, 43, 97, 99-103, 105-106, 134 and 135 will be pending in the application. Claims 1, 5, 27 and 43 are withdrawn from consideration. Claims 2, 134 and 135 are amended to require that the tumor expresses indoleamine-2,3-dioxygenase. Support for this amendment can be found in the specification, at page 20, lines 19-20. No new matter has been introduced by way of these amendments. Entry is respectfully requested.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 2, 99-101, 103, 105-106, and 135 are rejected under 35 U.S.C. § 112, first paragraph as not being enabled for methods of delaying the relapse or progression of a tumor other than a lung or a melanoma tumor comprising 1-methyl-D-tryptophan without the use of cyclophosphamide. As stated in the Office Action at page 6, the Examiner states that IDO-expressing tumors will have a higher likelihood of responding to the claimed methods. Applicants respectfully disagree. However, in order to advance prosecution, Applicants have amended the claims to recite that the tumor is an IDO-expressing tumor. Withdrawal of this rejection is therefore earnestly solicited.

Rejections under 35 U.S.C. § 103(a)

Claims 2, 99-101, 103, 105-106 and 134-135 are rejected as being obvious over Van Den Eynde et al. (WO 00/66764) in view of Peterson et al. ("Evaluation of Functionalized-Tryptophan Derivatives and Related Compounds as Competitive Inhibitors of Indoleamine-2,3-dioxygenase" 1994; Med. Chem. Res.; 3:531-544) and Karrer "Organic Chemistry" 1947, 3rd Ed., Elsevier Publishing Company, Inc., New York, pp 94-105). According to the Examiner, it

would have been obvious to one of ordinary skill in the art to practice the method of treating cancer of Van Den Eynde with the D isomer of 1-methyl-tryptophan as taught in Peterson. Applicants respectfully disagree.

As stated by the Examiner on page 7 of the Office Action, the factual inquiries set forth in *Graham* are applied for determining obviousness under 35 U.S.C. 103(a). Those factors are as follows:

1. Determining the scope and contents of the prior art
2. Ascertaining the difference between the prior art and the claims at issue
3. Resolving the level of ordinary skill in the pertinent art
4. Considering objective evidence present in the application indicating obviousness or non obviousness."

With respect to the scope and contents of the prior art, nowhere does the cited art teach or suggest using the D isomer of 1-methyl-tryptophan for the treatment of a subject to delay the progression of a tumor, or any other disease or condition for that matter. Furthermore, the differences between the prior art teaching of using the racemate and independently that the D and L isomers can be resolved is substantially different than the claims at issue which involve the *in vivo* delaying of the progression of a tumor. The Peterson reference reports merely testing the ability to inhibit purified intestinal IDO enzymatic activity *in vitro*, and even then the D isomer is significantly less potent than the L isomer. Additionally, the level of skill in the unpredictable pharmaceutical arts is high as has been recognized by the Federal Circuit numerous times.

Most importantly, the objective indicia of non-obviousness weigh heavily in favor of non-obviousness. That is to say, Peterson teaches away from using the D isomer of 1-methyl-tryptophan for pharmaceutical uses involving IDO inhibition. Specifically, Peterson teaches that

the L isomer is, by far, the more potent of the two isomers at inhibiting IDO enzymatic activity. Thus it is unexpected that the D isomer has more potent antitumor activity *in vivo*. As recognized by the Declaration under 37 C.F.R. §1.132 by Dr. William Malachowski (submitted herewith), one of ordinary skill in the art would have been motivated to use the more potent L isomer and not the D isomer for IDO inhibition based on the teaching of Peterson. Therefore, based on the *Graham* factors, the use of the 1-methyl-D-tryptophan is not obvious over Van Den Eynde and Peterson.

The Examiner cites *In re Adamson and Duffin,* 125 USPQ 233 (CCPA 1960) in support of his contention that the use of the D isomer of 1-methyl-tryptophan is obvious in view of the prior art teaching of the use of the racemate. However, contrary to the Examiner's assertion, the facts in Adamson are not analogous to the current facts. First of all, the claims at issue in *Adamson* were composition claims and not method claims. Applicants are not seeking a claim to 1-methyl-D-tryptophan in this application. Additionally and importantly, in *Adamson,* there was no prior art teaching away from using the claimed isomer. In *Adamson* the court found that it was "particularly expected" that the specific enantiomer would have the observed properties. In the current case, one of ordinary skill in the art would not have expected the enantiomer that was less potent in culture, the D isomer of 1-methyl-tryptophan, to be pharmaceutically superior for delaying the progression of a tumor *in vivo* as claimed in the present application. According to *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, a prior art reference needs to be considered as a whole, including the portions that would lead away from the claimed invention (*See* M.P.E.P. 2141.02.VI).

Furthermore, in more recent case law, in *Forrest Laboratories v. Ivax Pharmaceuticals, Inc.*, 501 F.3d 1263 (Fed. Cir. 2007) (copy attached) the Federal Circuit affirmed that the (+)

enantiomer of citalopram was not obvious over the known racemate when it was shown that the therapeutic properties of the (+) enantiomer were unexpected. The facts of the current case are more analogous to those in *Forrest Laboratories* in that the pharmaceutical superiority of the less potent D isomer was unexpected in view of the prior art.

Therefore, in light of the following, Applicants assert that the claims are non-obvious over the prior art. Withdrawal of this rejection is earnestly solicited.

In view of the foregoing, Applicant respectfully submits that no further impediments exist to the allowance of this application and, therefore, requests an indication of allowability. However, the Examiner is requested to call the undersigned if any questions or comments arise.

The Director is hereby authorized to charge any appropriate fees under 37 C.F.R. §§1.16, 1.17, and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 50-1283.

Dated: October 28, 2010

Respectfully submitted,
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Assignment is all-inclusive and it is not known what remedy would ensue if the protest were sustained. The protester is not required to affirmatively request only the minimal monetary relief in order to avoid "mootness." The judicial fashioning of appropriate relief, should the protest be sustained, is not before us. It is not correct to rule that the protest cannot be made at all.

Today's ruling of mootness has potentially broad consequences for government contracting, for it holds that if the losing bidder is pressed into insolvency while its protest is pending, the right to protest a wrongful award disappears. This is not correct law, and it subverts legislative policy. I respectfully dissent.

FOREST LABORATORIES, INC., Forest Laboratories Holding, Ltd., and H. Lundbeck a/s, Plaintiffs–Appellees,

v.

IVAX PHARMACEUTICALS, INC. and Cipla, Ltd., Defendants–Appellants.

No. 2007–1059.

United States Court of Appeals, Federal Circuit.

Sept. 5, 2007.

Rehearing Denied Oct. 12, 2007.

Background: Patentee and assignee brought action against manufacturer of generic drugs and its intended supplier alleging infringement of its patent for antidepressant drug, and manufacturer filed counterclaims of invalidity and unenforceability. The United States District Court for the District of Delaware, Judge Joseph J. Farnan, Jr., J., 438 F.Supp.2d 479, upheld patent's validity and enjoined manufacturer and supplier from infringing it. Manufacturer and supplier appealed.

Holdings: The Court of Appeals, Lourie, Circuit Judge, held that:

(1) finding that prior art reference in printed publication did not anticipate patent was not clearly erroneous;

(2) finding that patent was not invalid for obviousness was not clear error;

(3) finding that claim in reissue patent did not improperly broaden scope of claims was not clear error; and

(4) supplier was subject to injunction.

Affirmed as modified.

Schall, Circuit Judge, dissented in part and filed opinion.

1. Patents ⇐324.55(4)

Anticipation is question of fact that Court of Appeals reviews for clear error following bench trial.

2. Patents ⇐314(5)

Whether prior art reference is enabling is question of law based upon underlying factual findings in patent infringement action.

3. Patents ⇐69

District court's factual finding that prior art reference in printed publication was not enabling, and thus did not anticipate patent for antidepressant drug, was not clearly erroneous, even though reference described effects of various enantiomers of other drugs on uptake of serotonin in brain tissue and/or platelets, and mentioned racemate, where reference was pharmacology paper, not chemical paper, incorrectly predicted that other enantiomer for drug would be far more potent as serotonin reuptake inhibitor, and did not teach one of ordinary skill how to make drug.

4. Patents ⇐324.5, 324.55(4)

Obviousness of invention is question of law, reviewed de novo, based upon under-

lying factual questions, which are reviewed for clear error following bench trial.

5. Patents ⇐16.25

District court's finding that patent for antidepressant drug was not invalid for obviousness was not clear error, despite contention that person of ordinary skill in the art would have had reasonable expectation that one could separate drug's enantiomers, in light of evidence that it was unexpected that all therapeutic benefit of drug would reside in particular enantiomer, and that others failed to resolve drug without undue experimentation.

6. Patents ⇐141(3.1)

Change in reissue application that is only clerical does not necessarily broaden scope of claims and so does not render patent invalid. 35 U.S.C.A. § 251.

7. Patents ⇐141(3.1)

In determining whether reissue patent improperly broadened scope of original patent, comparison of scope of reissue claims with claims of original patent is matter of claim construction, and it is performed from perspective of one having ordinary skill in the art. 35 U.S.C.A. § 251.

8. Patents ⇐324.5, 324.55(3.1)

Whether claims of reissue patent impermissibly broaden scope of original patent is question of law that Court of Appeals reviews de novo based on underlying facts reviewed for clear error. 35 U.S.C.A. § 251.

9. Patents ⇐141(3.1)

District court's finding that claim in reissue patent for antidepressant drug did not improperly broaden scope of claims of original patent upon which it was based was not clear error, in light of evidence that reissue patent corrected typographical error in optical rotation sign that resulted in what one skilled in art would know was chemically impossible reaction. 35 U.S.C.A. § 251.

10. Federal Courts ⇐776, 814.1

Although standard of review for issuance and scope of injunction is abuse of discretion, whether injunction's terms fulfill mandates of governing rule is question of law that Court of Appeals reviews de novo. Fed.Rules Civ.Proc.Rule 65(d), 28 U.S.C.A.

11. Patents ⇐317

District court order enjoining generic drug manufacturer and its intended supplier from commercially manufacturing or selling "any products" that infringe patent was overly broad, and would be narrowed to encompass only approved drug, not remainder of products covered by patent. 35 U.S.C.A. § 271(e)(4)(B); Fed.Rules Civ. Proc.Rule 65(d), 28 U.S.C.A.

12. Patents ⇐317

Generic drug manufacturer's intended supplier was subject to injunction barring commercial manufacture or sale of approved drug, where supplier actively induced manufacturer's acts that would constitute direct infringement upon approval of abbreviated new drug application (ANDA). 35 U.S.C.A. § 271(e)(1), 271(e)(2).

Patents ⇐328(2)

4,136,193, 4,650,884. Cited.

Patents ⇐328(4)

34,712. Valid and Infringed.

John M. Desmarais, Kirkland & Ellis LLP, of New York, NY, argued for plaintiffs-appellees. With him on the brief were Peter J. Armenio, Gerald J. Flattmann, Jr., Ellen A. Scordino, and Anne S. Toker.

Henry C. Dinger, Goodwin Proctor LLP, of Boston, MA, argued for defen-

dants-appellants. With him on the brief was Francis C. Lynch. Of counsel on the brief were Jeffrey S. Ward, and Thomas P. Heneghan, Michael Best & Friedrich LLP, of Madison, WI.

Before LOURIE, Circuit Judge, FRIEDMAN, Senior Circuit Judge, and SCHALL, Circuit Judge.

Opinion for the court filed by Circuit Judge LOURIE. Opinion concurring as to parts I through IV.A and dissenting as to part IV.B filed by Circuit Judge SCHALL.

LOURIE, Circuit Judge.

Ivax Pharmaceuticals, Inc. ("Ivax") and Cipla, Ltd. ("Cipla") appeal from the order of the United States District Court for the District of Delaware entering judgment upholding the validity of United States Reissue Patent 34,712 ("the '712 patent") in favor of Forest Laboratories, Inc., Forest Laboratories Holding, Ltd., and H. Lundbeck A/S (collectively "Forest") and enjoining Ivax and Cipla from infringing the '712 patent. We affirm the district court's entry of judgment on validity and its entry of an injunction as to both Ivax and Cipla, but we modify the injunction to apply only to escitalopram oxalate.

BACKGROUND

Ivax filed Abbreviated New Drug Application 76–765 ("the ANDA") at the Food and Drug Administration, pursuant to 21 U.S.C. § 355(j) (§ 505(j) of the Federal Food, Drug, and Cosmetic Act), for approval to market generic tablets containing 5, 10, or 20 milligrams of escitalopram oxalate ("EO"). The ANDA certified, pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), that the claims of the '712 patent are invalid and/or not infringed by the manufacture, use, or sale of the products for which approval was sought. Cipla is the intended supplier of EO for Ivax and contributed information for the filing of the ANDA. Forest filed suit on September 22, 2003, alleging that Ivax's filing of the ANDA infringed the '712 patent under 35 U.S.C. § 271(e)(2)(A).[1] Ivax filed its answer on October 15, 2003, denying infringement and counterclaiming for invalidity of the '712 patent. Forest later amended its complaint to add Cipla as a defendant on May 27, 2004.

The '712 patent issued on August 30, 1994 and relates, *inter alia*, to a substantially pure (+)-enantiomer of citalopram (also referred to as "escitalopram") and nontoxic acid additional salts thereof. Stereoisomers are compounds that contain the same constituent atoms and the same bonding between those atoms but have different spatial arrangements. Enantiomers are stereoisomers that are nonsuperimposable mirror images of one another. Enantiomers accordingly exhibit different optical activity; the enantiomer that rotates a plane of polarized light in the clockwise direction is the (+)enantiomer; the enantiomer that rotates a plane of polarized light in the counterclockwise direction is the (-)-enantiomer. Enantiomers may also be designated as the S-enantiomer and the R-enantiomer according to a different criterion relating to the location of the chiral centers. In the case of citalopram, the (+)-enantiomer is also the S-enantiomer. A mixture of equal amounts of two enantiomers is

1. 35 U.S.C. § 271(e)(2)(A) provides:
It shall be an act of infringement to submit an application under section 505(j) of the Federal Food, Drug, and Cosmetic Act or described in section 505(b)(2) of such Act for a drug claimed in a patent or the use of which is claimed in a patent if the purpose of such submission is to obtain approval under such Act to engage in the commercial manufacture, use, or sale of a drug or veterinary biological product claimed in a patent or the use of which is claimed in a patent before the expiration of such patent.

called a racemic mixture or a racemate, and separating the two enantiomers from a racemate is referred to as resolving the compound. Forest also owned the now expired U.S. Patent 4,136,193 on the racemic form of citalopram and U.S. Patent 4,650,884 that claims a method for making racemic citalopram using an intermediate racemic 1,4–diol.

EO, which is the oxalate salt form of escitalopram, is one of the compounds encompassed by the claims of the '712 patent. It is an antidepressant by virtue of being a selective serotonin reuptake inhibitor and is the active ingredient in Forest's Lexapro® branded drug. Forest has alleged that Ivax and Cipla infringed claims 1, 3, 5, 7, 9 and 11 of the '712 patent by filing the ANDA. Independent claim 1 of the '712 patent reads as follows:

> A compound selected from substantially pure (+)–1–(3–Dimethylaminopropyl)–1–(4'–fluorophenyl)–1,3–dihydroisobenzofuran–5–carbonitrile and non-toxic acid addition salts thereof.

'712 patent col.10 ll.31–34. Dependent claim 11 recites a method of preparing the compound of claim 1 by cyclizing an intermediate diol.

The parties stipulated to a specific claim construction for the primary disputed term in the '712 patent, and, based on that agreement, the parties further stipulated that the proposed products included in the ANDA infringe claims 1, 3, 5, 7, and 9 of the '712 patent and that the proposed process for making those products infringes claim 11. Thus, the district court was only required to reach a determination with respect to the counterclaims, including those asserting that the claims are invalid for anticipation and obviousness, and that they were improperly broadened through reissue.

After a bench trial, the district court issued its decision on July 13, 2006, concluding that Ivax and Cipla had failed to prove that the '712 patent is invalid as anticipated. Specifically, the court found that an article by Donald F. Smith ("Smith") entitled *The Stereoselectivity of Serotonin Uptake in Brain Tissue and Blood Platelets: The Topography of the Serotonin Uptake Area* ("Smith reference") did not anticipate claim 1 of the '712 patent because it did not disclose "substantially pure" escitalopram as claimed in claim 1 and it did not enable a person having ordinary skill in the art to obtain that compound. The court found that chiral High Performance Liquid Chromatography ("HPLC") was a relatively new and unpredictable technique at the time of the invention and that Smith had worked with the founder of the field of chiral HPLC to separate the enantiomers of citalopram near the time of the invention, but had failed in his efforts. The court also found that a team of chemists at Lundbeck had unsuccessfully attempted to use chiral HPLC to resolve citalopram for two years and that Dr. Danishefsky, Forest's medicinal chemistry expert, had unsuccessfully tried to resolve compounds with HPLC in the mid–1980's. The court also found that an inventor of the '712 patent, Dr. Bogeso, had conducted numerous experiments attempting to resolve racemic citalopram through the method of diasteriomeric salt formation, but had also failed. Finally, the court found that Dr. Bogeso only attempted to resolve citalopram using a diol intermediate, as recited in claim 11 of the '712 patent, as a last resort and that others of skill in the art would have similarly hesitated because there was a real possibility that the resolved intermediate would re-racemize during the attempt to convert it from the diol intermediate enantiomer to the desired citalopram enantiomer. Thus, the court found that attempting to separate the enantiomers of citalopram based on the knowledge of one of ordinary skill in

the art would have required undue experimentation and that the Smith reference was therefore not enabled.

Next, the district court concluded that Ivax and Cipla had failed to prove by clear and convincing evidence that any of the asserted claims of the '712 patent were obvious. The court found that one of ordinary skill in the art at the time of the invention would generally have been motivated to develop new compounds rather than undertake the difficult and unpredictable task of resolving a known racemate. The court further found that a person of ordinary skill attempting to resolve racemic citalopram would have had no reasonable expectation of success for reasons similar to those discussed with respect to enablement of the Smith reference. With respect to the method of claim 11 of the '712 patent, the court found that none of the articles relied upon by Ivax and Cipla described the particular types of reactions claimed (viz., "a Mosher ester serving as a leaving group for a ring closure of a Diol Intermediate," "an enantioconserving ring closure of a diol containing a tertiary amine to form a tetrahydrofuran," or "an enantioconserving cyclization reaction of the type needed to convert a tertiary amine like any enantiomerically pure Diol Intermediate into substantially pure (+)-citalopram"). The court also found that secondary considerations of commercial success, unexpected results, and copying by others supported the validity of the claims.

In addition, the district court found that claim 11 of the '712 patent was not invalid for impermissible broadening during reissue. During the reissue proceeding that resulted in the '712 patent, claim 11 was corrected to claim a method of converting a(-)-diol intermediate to (+)-citalopram, rather than using a(+)-diol intermediate as shown in the original patent claim. The court found that, given the specific description of the process in the specification, this change amounted to correction of a typographical error. In other words, the court found that the mistake would have been clear to one of ordinary skill in the art reviewing the patent, and therefore that it did not constitute a change in scope from the original claim.

The court entered judgment in accordance with its opinion on November 3, 2006 and at the same time enjoined both Ivax and Cipla "from commercially making, using, offering to sell or selling within the United States, or importing into the United States any products that infringe the '712 patent, including the escitalopram oxalate products referred to in the Abbreviated New Drug Application No. 76–765 until such time as the '712 patent expires." Ivax and Cipla timely appealed. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

DISCUSSION

I. *Anticipation*

On appeal, Ivax and Cipla argue that the Smith reference clearly anticipates claim 1 of the '712 patent because it discusses and analyzes the efficacy of various drug enantiomers and predicts that one citalopram enantiomer will be more potent as a serotonin reuptake inhibitor than the other. Ivax and Cipla further argue that one of ordinary skill in the art would have known at the time of the invention to use diasteriomeric salt formation to resolve citalopram. Specifically, a person of skill in the art would have used the method described in the Wilen reference to resolve the racemic intermediate diol into its enantiomers and the method in the Jacobus reference (Williamson ether synthesis) to convert the diol enantiomer (by cyclizing the ether ring) to (+)-citalopram. Ivax and Cipla add that Dr. Bogeso's ability to resolve citalopram on his first try after

starting with the diol intermediate is further compelling evidence that only routine experimentation was required to separate the enantiomers.

In response, Forest argues that the Smith reference does not disclose "substantially pure" (+)-citalopram. Forest also argues that the testimony of the experts and the repeated failures of Dr. Bogeso and others to resolve citalopram into its enantiomers support the district court's determination that the Smith reference was not enabled for (+)-citalopram. Forest also states that the court was correct to conclude that a person of ordinary skill would have viewed the difficulty in resolving the diol intermediate rather than citalopram itself as significant and a deterrent. In addition, Forest argues that even if a person of skill in the art were to consider using the diol, the Wilen and Jacobus references do not involve compounds with structures similar enough to the citalopram diol intermediate so that a person of ordinary skill would rely upon them to predict the results of a reaction with that compound. More specifically, Forest argues that neither reference discloses a cyclizing reaction involving a compound, like the citalopram diol, that has a resident tertiary amine or a benzylic alcohol.

[1, 2] Anticipation is a question of fact that we review for clear error following a bench trial. *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 457 F.3d 1293, 1304 (Fed.Cir.2006). "Under the clear error standard, the court's findings will not be overturned in the absence of a definite and firm conviction that a mistake has been made." *Impax Labs., Inc. v. Aventis Pharm. Inc.*, 468 F.3d 1366, 1375 (Fed.Cir. 2006) (quotation omitted). "Whether a prior art reference is enabling is a question of law based upon underlying factual findings." *Id.* at 1382 (quoting *Minn. Mining & Mfg. Co. v. Chemque, Inc.*, 303 F.3d 1294, 1301 (Fed.Cir.2002)).

[3] We agree with Forest that the district court's factual findings relating to enablement of the Smith reference are not clearly erroneous, and, based upon those findings, we find no error in the district court's conclusion that the Smith reference is not enabled with respect to (+)-citalopram. The Smith reference is a pharmacology paper, not a chemical paper. It describes the effects of various enantiomers of particular drugs (not including (+)-citalopram) on the uptake of serotonin in brain tissue and/or platelets. It mentions racemic citalopram ("also of interest") and shows its structure, but predicts, incorrectly, that the R-enantiomer (the (-)-enantiomer for citalopram, not the one claimed in the '712 patent) should be far more potent as a serotonin reuptake inhibitor. Because a racemate does encompass its two enantiomers, it in effect does state that there is a(+)-enantiomer of citalopram, but it does not tell how to obtain it. A reference that is not enabling is not anticipating. *Elan Pharm., Inc. v. Mayo Found. For Med. Educ. & Research*, 346 F.3d 1051, 1054 (Fed.Cir.2003). The Smith reference, as a pharmacology paper, thus does not enable the preparation of the (+)-enantiomer of citalopram.

Ivax and Cipla acknowledge that the Smith reference itself does not teach one of ordinary skill how to make (+)-citalopram, but their arguments that it is enabled by other references are largely a recounting of the testimony favorable to their theory of the case without explanation as to why we should have a definite and firm conviction that mistakes were made by the district court in its fact-finding. In other words, they do not inform us why the district court was not entitled to rely on the evidence favorable to Forest or demonstrate that the evidence favorable to them heavily outweighed the evidence favorable to Forest. Such evidence includes the failures of various scientists to resolve

citalopram as recited above. Given Ivax and Cipla's failure to disturb the detailed and thorough factual findings underlying the district court's decision, we see no error in the finding that the Smith reference does not enable one of ordinary skill to make (+)-citalopram and hence that the Smith reference does not anticipate claims to (+)-citalopram.

II. *Obviousness*

Ivax and Cipla argue that (+)-citalopram was obvious in light of racemic citalopram and descriptions of techniques available to separate enantiomers from their racemates. Further, they argue that the general expectation in the art that one enantiomer would be more potent than the other provided reason for a person of ordinary skill in the art to isolate the enantiomers. For reasons similar to those discussed with respect to their argument that the Smith reference was enabled, Ivax and Cipla contend that a person of ordinary skill in the art would have had a reasonable expectation that one could separate the enantiomers of citalopram. Ivax and Cipla also argue that Lexapro's® commercial success was due to aggressive marketing rather than any alleged superiority of the drug to alternatives and that it did not possess unexpectedly superior properties. Ivax and Cipla also argue that claims 3, 5, 7, and 9 represent only obvious variations on claim 1 with no elements that are not standard in medicinal chemistry and that claim 11 represents the obvious way of resolving citalopram in light of the teaching of the Wilen and Jacobus references.

In response, Forest argues that any prima facie obviousness based on racemic citalopram was rebutted by the evidence demonstrating the difficulty of separating the enantiomers and the unexpected properties of (+)-citalopram. Forest argues that it was unexpected that all of the therapeutic benefit of citalopram would reside in the (+)enantiomer, resulting in escitalopram having twice the potency of racemic citalopram. Forest also argues that the district court was entitled to credit evidence that a person of ordinary skill in the art would not easily have turned to the diol intermediate to attempt resolution of racemic citalopram both because of the uncertainty involved and because Wilen and Jacobus describe compounds less complex than those necessary here to resolve the diol intermediate and then convert the (-)-diol enantiomer to escitalopram.

[4] "Obviousness is a question of law, reviewed de novo, based upon underlying factual questions which are reviewed for clear error following a bench trial." *Leapfrog Enter., Inc. v. Fisher–Price, Inc.*, 485 F.3d 1157, 1160 (Fed.Cir.2007) (quoting *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1289 (Fed.Cir.2006)).

[5] We agree with Forest that the district court's key factual findings underlying its conclusions on obviousness are not clearly erroneous, and, based upon those findings, we find no error in the court's conclusion that the asserted claims of the '712 patent are not invalid for obviousness. As with their arguments on anticipation, Ivax and Cipla mainly emphasize the evidence that is favorable to their desired outcome without addressing the evidence favorable to Forest. The latter includes the failure of the inventors and others to resolve citalopram without undue experimentation and the testimony of Forest's experts. The district court applied the *Graham* factors to conduct a thorough analysis of the evidence, and we find no clear error on facts and no error of law. *See Graham v. John Deere Co.*, 383 U.S. 1, 86 S.Ct. 684, 15 L.Ed.2d 545 (1966). These findings fully support the conclusion that the claimed subject matter would not have been obvious to one of ordinary skill in the art.

III. *Broadening Reissue*

Ivax and Cipla argue that claim 11 of the '712 patent is invalid because it represents a broadening of original claim 11. They argue that the change in the optical rotation sign of the diol intermediate in claim 11 during reissue was clearly a broadening of the claim because the claim now covers a process beginning with a different enantiomer. Ivax and Cipla also argue that a typographical error may nonetheless be broadening and that a typographical error must be evident to the general public in order to serve the public notice function of patents. In response, Forest argues that the district court correctly determined that the reissue application corrected a typographical error that was readily apparent to one of ordinary skill in the art reviewing the patent and therefore did not result in any change in the scope of the patent.

> The reissue statute reads as follows:
>
> Whenever any patent is, through error without any deceptive intention, deemed wholly or partly inoperative or invalid, by reason of ... the patentee claiming more or less than he had a right to claim in the patent, the Director shall ... reissue the patent for the invention disclosed in the original patent ... for the unexpired part of the term of the original patent.... No reissued patent shall be granted enlarging the scope of the claims of the original patent unless applied for within two years from the grant of the original patent.

35 U.S.C. § 251.

[6] The '712 reissue patent resulted from an application filed more than two years after the grant of the original patent, and the claims of a reissue patent filed after that date are invalid if they enlarge the scope of the original claims. *See* 35 U.S.C. § 282; *Quantum Corp. v. Rodime PLC*, 65 F.3d 1577, 1583 (Fed.Cir.1995). However, a change in a reissue application that is only clerical does not necessarily broaden the scope of the claims and so does not render the patent invalid. The question before us is whether the change effected in the reissue application here broadened the scope of claim 11 or merely clarified or corrected the original claim.

[7, 8] Comparison of the scope of the reissue claims with the claims of the original patent is a matter of claim construction, and it is performed from the perspective of one having ordinary skill in the art. *See Pannu v. Storz Instruments, Inc.*, 258 F.3d 1366, 1370 (Fed.Cir.2001); *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed.Cir. 2005) (en banc). Whether the claims of a reissue patent violate 35 U.S.C. § 251 is a question of law that we review *de novo* based on underlying facts reviewed for clear error. *Medtronic, Inc. v. Guidant Corp.*, 465 F.3d 1360, 1373 (Fed.Cir.2006).

[9] We agree with Forest that the change in the optical rotation sign for the diol intermediate in claim 11 of the '712 patent did not broaden the scope of the claim. The patent specification supports, even compels, this conclusion. In Reaction Scheme I, the process begins with a racemic mixture of the diol intermediate. *See* '712 patent col.5 ll.41–42. The diagram of Reaction Scheme I reinforces that conclusion because it includes a notation next to the diagram of the diol intermediate that reads "(+) *and* (-)." '712 patent (emphasis added). The patent then describes a reaction sequence that results in production of "the ester as a diastereomeric mixture." *Id.* at col.5 ll.47–48. It is the diastereomeric mixture of an ester (of a monoalcohol) that is then subjected to HPLC to produce an enantiomerically pure compound that can be converted into the desired (+)-citalopram end product. *Id.* at col.5 ll.47–59. Further, as found by the district court, because Reaction Scheme I begins with the racemate of the

diol intermediate, the patent is ambiguous as to which enantiomer of the diol intermediate is actually converted to (+)-citalopram.

In contrast, while the description of Reaction Scheme II also begins with the racemate of the diol intermediate, it is the diol intermediate itself that is resolved to produce an enantiomerically pure product compound. *Id.* at col.6 ll.8–33. The description also specifically describes using the (-)-diol intermediate to produce (+)citalopram. *Id.* at col.6 ll.29–42. Further support is again provided by the diagram of Reaction Scheme II, which includes a notation that reads "(-) *or* (+)" next to the structural diagram of citalopram. '712 patent (emphasis added). Thus, the enantiomeric labeling for the end product is reversed from that of the starting compound. Given this plain reading and the additional supporting expert testimony also relied upon by the district court, we see no error in the district court's finding that a person of ordinary skill in the art reviewing the patent would find the error in claim 11 relating to the optical sign of the diol intermediately apparent. The diagram of Reaction Scheme II makes clear that it is the (-)-diol that is converted to (+)-citalopram and that the correction in the claim corresponds to the disclosure in the specification. We therefore agree that the change in the optical sign during reissue does not represent a change of claim scope, but merely a correction of the claim to be consistent with the disclosure of the specification.

IV. *The Scope of the Injunction*

Ivax and Cipla argue that the language of the injunction is overly broad in extending to "any products that infringe the '712 patent." Also, they argue that the artificial act of infringement created by 35 U.S.C. § 271(e)(2)(A) is narrow and that Cipla's provision of information to Ivax for its filing of the ANDA is not an act of infringement. Ivax and Cipla further argue that the injunction granted by the district court violates our holding in *International Rectifier Corp. v. IXYS Corp.*, 383 F.3d 1312, 1316 (Fed.Cir.2004). Forest responds that the injunction is sufficiently narrowly defined because of the infringement stipulation of the parties and the detailed record. Forest also argues that because Cipla will manufacture and import the EO products described in the ANDA if it is approved, Cipla may properly be enjoined for inducement of infringement.

A. *Scope of Products*

[10] We do not agree with the scope of the district court's injunction that includes products other than escitalopram oxalate. "Although the standard of review for the issuance and scope of an injunction is abuse of discretion, whether the terms of the injunction fulfill the mandates of Federal Rule of Civil Procedure 65(d) is a question of law that this court reviews de novo." *Signtech USA, Ltd. v. Vutek, Inc.*, 174 F.3d 1352, 1356 (Fed.Cir.1999). In *International Rectifier*, we held that "the only acts [an] injunction may prohibit are infringement of the patent by the adjudicated [products] and infringement by [products] not more than colorably different from the adjudicated [products]. 383 F.3d at 1316. In order to comply with Rule 65(d), the injunction should explicitly proscribe only those specific acts."

[11] Here, the '712 patent covers a range of products beyond those described in the ANDA. The statute, 35 U.S.C. § 271(e)(4)(B), provides that "injunctive relief may be granted against an infringer to prevent the commercial manufacture, use, offer to sell, or sale within the United States or importation into the United States of an approved drug." Thus, while the injunction may properly extend to the

"approved drug," it should not extend to the remainder of the products covered by the patent. The injunction is therefore modified to delete the language "any products that infringe the '712 patent, including."

B. *Inclusion of Cipla*

However, we find that it was not inappropriate for the district court to include Cipla within the scope of the injunction. Section 271(e)(2) may support an action for induced infringement. *Allergan, Inc. v. Alcon Labs., Inc.*, 324 F.3d 1322, 1331 (Fed.Cir.2003). "The only difference in the analysis of a traditional infringement claim and a claim of infringement under section 271(e)(2) is the timeframe under which the elements of infringement are considered." *Id.* An inquiry into induced infringement focuses on the party accused of inducement as the prime mover in the chain of events leading to infringement. Here, we do not know if Cipla first approached Ivax or vice versa, but the plan to manufacture, import, market, and sell the EO products described in the ANDA was undoubtedly a cooperative venture, and Cipla was to manufacture and sell infringing EO products to Ivax for resale in the United States. Under the standards for inducement which we apply to 35 U.S.C. § 271(b), Cipla has therefore actively induced the acts of Ivax that will constitute direct infringement upon approval of the ANDA, and it was thus not inappropriate for the district court to include Cipla within the scope of the injunction.

[12] The dissent asserts that § 271(e)(1) exempts Cipla from being enjoined with Ivax. We disagree. Cipla is providing information, and will provide material, that Ivax will use to obtain FDA approval. Up to that point, there is indeed no infringement. And, in fact, Ivax is not currently liable for infringement, as long as it is only pursuing FDA approval, not commercially manufacturing or selling the infringing product. However, just as Ivax will be liable for, and hence is being enjoined from, the commercial exploitation of escitalopram when it is approved by the FDA and during the life of the patent, so should Cipla be enjoined. They are partners. Cipla would be contributing to the infringement by Ivax, so the injunction should cover both partners. It is true that, as the dissent states, § 271(e)(2) defines Ivax's filing of its ANDA as an infringement, and Cipla did not file the ANDA; however, when the question of an injunction against commercial activity arises, Cipla is as culpable, and hence entitled to be enjoined, as Ivax.

CONCLUSION

For the reasons stated, we affirm the district court's grant of judgment of no invalidity of the '712 patent and the entry of injunction, as modified herein, as to both Ivax and Cipla pursuant to the stipulation of infringement.

AFFIRMED

SCHALL, Circuit Judge, dissenting-in-part.

I join the court's opinion insofar as it (i) affirms the judgment of non-invalidity of the '712 patent and (ii) modifies the scope of the injunction issued by the district court. However, I respectfully dissent from the court's opinion insofar as it affirms the district court's entry of an injunction as to Cipla.

Ivax filed its ANDA seeking approval to market generic tablets containing escitalopram oxalate. *See Forest Labs., Inc. v. Ivax Pharms., Inc.*, 438 F.Supp.2d 479, 484

(D.Del.2006). Under the statutory framework set forth by Congress:

> It shall be an act of infringement to submit—
>
> (A) an application under section 505(j) of the Federal Food, Drug, and Cosmetic Act or described in section 505(b)(2) of such Act for a drug claimed in a patent or the use of which is claimed in a patent, or
>
> (B) an application under section 512 of such Act or under the Act of March 4, 1913 (21 U.S.C. 151–158) for a drug or veterinary biological product which is not primarily manufactured using recombinant DNA, recombinant RNA, hybridoma technology, or other processes involving site specific genetic manipulation techniques and which is claimed in a patent or the use of which is claimed in a patent,
>
> if the purpose of such submission is to obtain approval under such Act to engage in the commercial manufacture, use, or sale of a drug or veterinary biological product claimed in a patent or the use of which is claimed in a patent before the expiration of such patent.

35 U.S.C. § 271(e)(2). By its terms, the statute limits the act of infringement to the filing of an ANDA application. At the same time, 35 U.S.C. § 271(e)(4)(B) provides that "injunctive relief may be granted *against an infringer* to prevent the commercial manufacture, use, offer to sell, or sale within the United States or importation into the United States of an approved drug or veterinary biological product." (Emphasis added).

In interpreting a statute, we presume that Congress intended to give words their ordinary meanings. *Asgrow Seed Co. v. Winterboer*, 513 U.S. 179, 187, 115 S.Ct. 788, 130 L.Ed.2d 682 (1995). In § 271(e)(2), Congress chose to employ the clause "[i]t shall be an act of infringement to submit." The plain language of § 271(e)(2) thus compels the conclusion that an action for infringement may lie based upon the filing of an ANDA. By filing its ANDA, Ivax committed an act constituting infringement under § 271(e)(2) and, as an infringer, was properly enjoined under § 271(e)(4)(B).

Cipla provided information to Ivax that was included in the ANDA, and if the ANDA were approved, Cipla would manufacture the escitalopram oxalate used in the proposed generic drugs. *Forest*, 438 F.Supp.2d at 484. In contrast to what IVAX did in this case, Cipla's involvement—limited to providing information to IVAX that was included in the submission of the ANDA—seems akin to the activity protected by paragraph (e)(1) of the statute, which provides that:

> It shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention ... solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products.

35 U.S.C. § 271(e)(1). The Supreme Court has stated that "§ 271(e)(1)'s exemption from infringement extends to all uses of patented inventions that are reasonably related to the development and submission of *any* information under the [Federal Food, Drug, and Cosmetic Act]." *Merck KGaA v. Integra Lifesciences I, Ltd.*, 545 U.S. 193, 202, 125 S.Ct. 2372, 162 L.Ed.2d 160 (2005). In short, Congress made it an act of infringement to file an ANDA, but exempted from infringement acts reasonably related to the development

and filing of an ANDA, such as those of Cipla here.

In holding that it was not inappropriate for the district court to include Cipla within the scope of the injunction, the court relies on *Allergan, Inc. v. Alcon Labs., Inc.*, 324 F.3d 1322 (Fed.Cir.2003), for the proposition that § 271(e)(2) may support an action for induced infringement. Maj. op. at 1272. I think *Allergan* is distinguishable on its facts. In *Allergan*, we held as a general matter that § 271(e)(2) may support an action for induced infringement.[1] However, in *Allergan* the defendant was the party that submitted the ANDA. 324 F.3d at 1332 ("[S]ummary judgment of non-infringement under section 271(e)(2)[ ] is inappropriate where the plaintiff can demonstrate the existence of a genuine issue of material fact with respect to the claim that the *ANDA filer* will induce infringement of its patent upon approval of the ANDA." (emphasis added)). In other words, the court was presented with the question of whether § 271(e)(2) may support an action where the ANDA filer would induce infringement if the ANDA were approved.

I am unable to agree that *Allergan* supports the proposition that, standing alone, what Cipla did here (providing information used in the filing of an ANDA) can form the basis for a cause of action under § 271(e)(2). In my view, that proposition goes beyond the language of § 271(e)(2). Accordingly, I respectfully dissent from that part of the court's opinion that affirms the district court's action enjoining Cipla.

1. In *Allergan*, a drug manufacturer, Allergan, who held a patent for a method of using a specified drug for a particular purpose brought an infringement action against two competitors, Alcon and Bausch & Lomb, who filed ANDAs seeking approval for the production of a generic version of the drug for a use different from the method of use of the drug claimed in the patent. Allergan brought its suit under 35 U.S.C. § 271(e)(2), alleging that if the FDA approved Alcon's and Bausch & Lomb's ANDAs, Alcon and Bausch & Lomb would induce doctors to infringe Allergan's patents by prescribing the drug for the patented method of use and would induce patients to infringe by using the drug for the patented method of use.

AUTOMOTIVE TECHNOLOGIES INTERNATIONAL, INC., Plaintiff/Counterclaim Defendant–Appellant,

v.

BMW OF NORTH AMERICA, INC., CK Electronics, Incorporated, Conti Temic Microelectronic, GmbH, and Temic Automotive of North America, Incorporated, Defendants,

and

DaimlerChrysler Corporation, Ford Motor Company, Honda Motor Company Limited, American Honda Motor Company, Incorporated, Hyundai Motor Company, Hyundai Motor America, Mazda Motor of America, Inc., Saab Cars USA, Inc., Siemens Automotive Corporation, and Toyota Motor Sales USA, Inc., Defendants/Counterclaimants–Appellees,